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Short-term clinico-radiographic response to super-selective intra-arterial cerebral infusion of Bevacizumab for the treatment of vestibular schwannomas in Neurofibromatosis type 2

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**Short-term Clinico-radiographic Response to Superselective
Intraarterial Cerebral Infusion of Bevacizumab for the Treatment of
Vestibular Schwannomas in Neurofibromatosis Type 2**

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There are no conflicts of interest in this study.

**Short-term Clinico-radiographic Response Superselective Intra-arterial
Bevacizumab for the Treatment of Vestibular Schwannomas in Neurofibromatosis
Type 2**

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Abstract

Neurofibromatosis type 2 (NF2) is an autosomal dominant syndrome with a prevalence of approximately 1 in 30,000. NF 2 is characterized by bilateral vestibular schwannomas, as well as meningiomas, ependymomas and gliomas. Currently, surgical resection and radiotherapy represent the mainstay of treatment, although new studies suggest a role for certain chemotherapeutic agents. Intravenous (IV) administration of Bevacizumab (Avastin, Genetech Pharmaceuticals) has been shown to be active in the treatment of vestibular schwannomas. The IV route of administration, however, carries a risk of known systemic side effects such as bowel perforation, wound dehiscence and pulmonary embolism. In addition, the percentage of drug that reaches the tumor site may be restricted by the blood tumor barrier (BTB). In this report we describe the super-selective intra-arterial infusion of Bevacizumab following blood brain barrier disruption for the treatment of vestibular schwannomas in three patients with Neurofibromatosis type 2. It represents the first time such a technique has been performed for this disease. Additionally, this method of drug delivery may have important implications in the treatment of patients with vestibular schwannomas associated with Neurofibromatosis type 2.

Introduction

Neurofibromatosis type 2 (NF2) is an autosomal dominant syndrome with a prevalence of approximately 1 in 30,000.[1] NF 2 is characterized by bilateral vestibular schwannomas (VS), as well as meningiomas, ependymomas and gliomas. In NF2 a mutation in Chromosome 22q11-13 leads to a deficiency or defect of the Merlin protein,

normally a tumor suppressor.[2] The lack of or deficiency in Merlin leads to a lack of tumor suppression and, thus, the characteristic tumors of neurofibromatosis.

The most profound effect of NF 2 is the characteristic bilateral VS that lead to profound progressive hearing loss by an early age.[1,2] Traditionally, treatment options for sporadic VS include surgical removal or radiation therapy.[3] While these have been shown to control tumor growth, they can lead to further significant hearing loss in the affected ear, as well as facial nerve weakness, trigeminal neuropathy, vestibular dysfunction and an increased risk for development of secondary malignancies later in life. However, in patients with NF2 presenting with bilateral VS, the risks become even greater. These patients often have significant pre-operative hearing loss and surgical intervention may only worsen their deficits. In addition, both surgical and radiation therapy have been shown to have poor rates of tumor control in VS.[4,5] Recently, the anti-vascular endothelial growth factor Bevacizumab (BV) has been assessed for its ability to control tumor growth in NF2 patients with untreatable VS.[6-8]

Vascular endothelial growth factor (VEGF), a signal protein that stimulates angiogenesis and vessel permeability, has been shown to be associated with tumor growth of VS in NF2 patients.[9] Multiple groups have recently shown that administration of intravenous BV, a humanized monoclonal antibody against VEGF, with a concentration of 5mg/kg biweekly can lead to tumor regression and improved hearing in patients with untreatable VS. The tumor volume reduction is also in accordance with a recently published human VS xenograft model in mice showing that the tumor growth rate decreased by an average of 50%, and the survival of the treated mice was prolonged by at least 50% after intravenous treatment with 10mg/kg BV.[10] Our group

hypothesized that intra-arterial BV would increase concentrations of the drug via local delivery of the anti-VEGF compound into the VS, thus leading to further reduction in tumor size and improvement in overall hearing, specifically word discrimination, in patients with NF 2.

Recently, we have published the technical feasibility of super-selective intra-arterial cerebral infusion (SIACI) of mannitol followed by BV for treatment of recurrent malignant supratentorial disease.[11-14] The protocol for selective infusion includes focal disruption of the BTB and high-dose first-pass infusion of the chemotherapy directly to the target. Given the preliminary data using IV BV in the treatment of VS, we wanted to test the hypothesis that SIACI of BV after BTB disruption would be effective in the treatment of VS in patients with NF 2.

This report details the protocol and technique of using endovascular SIACI of BV following blood brain barrier disruption in three patients with VS with NF 2 (Table 1). If proven both safe and effective in larger trials, this novel delivery method may offer a better way to treat VS in this patient population.

Case Presentations

Case 1

Medical History and Postinterventional Follow-up

A 56-year-old male with a history of neurofibromatosis type 2 presented with complete right-sided hearing loss for 1 year and a progressive intermittent hearing loss and ringing on the left side. The patient did not present with either dizziness or ataxia. An MRI revealed bilateral T1 hypointense, T2 hypointense, enhancing masses within the cerebellopontine angles with extension into the internal auditory canals. The tumors,

with typical radiographic findings for VS, measured 1.3 x 1.9 x 1.2 cm on the right and 1.4 x 2.0 x 1.1 cm on the left side, respectively. (Figure 1A) The decision to treat the left VS was made to improve the patient's progressive intermittent hearing loss and after confirmed consent, the patient was treated by SIACI BV. Since the right-sided hearing loss was already present for over one year, no indication for treatment for this side was made at this time. After successful intra-arterial intervention, the patient presented with a progressive hearing improvement of his left ear starting 1 week post treatment. Post-contrast T1 MRI 1 month after treatment of the lesions measured 1.3 x 1.9 x 1.2 cm on the right and 1.4 x 2.0 x 1.1 cm on the left side with a tumor volume reduction of 11% of the right and 19% of the left side, respectively. No adverse effects with regard to the IA BV administration were seen.

Superselective Intra-arterial Cerebral Infusion Treatment

The patient was placed under general anesthesia and anticoagulated with heparin. A 5F guide catheter was placed into the left vertebral artery (VA), and then an Excelsior SL 10 microcatheter (Target Therapeutics/Boston Scientific, Fremont, CA) with a 45 degree angle was advanced over a Synchro 2 soft microwire into the left anterior inferior cerebellar artery (AICA). The microwire was then carefully removed. Then, 10 cc of 25% mannitol was infused through the microcatheter over a period of 2 minutes. Post mannitol infusion, posteroanterior (PA) and lateral projections of the left AICA demonstrated normal anterograde flow. No tumor blush of the VS was detected. After blood brain barrier disruption, 17 cc of BV (15 mg/kg) was infused through the same microcatheter over 20 minutes. Post infusion angiography was performed demonstrating

normal antegrade flow (Figure 1B). Using the same technique, a microcatheter was positioned in the left external carotid artery (ECA) and 10 cc of 25% mannitol was infused over a period of 2 minutes. Post mannitol infusion, PA and lateral projections of the left middle meningeal artery (MMA) demonstrated normal antegrade flow. Then, 17 cc of BV (15 mg/kg) was infused through the microcatheter over 20 minutes. Post infusion angiography confirmed the microcatheter tip still in the left MMA. The microcatheter was withdrawn to the left ECA. Then, 17 cc of BV (15 mg/kg) was infused through the microcatheter over 20 minutes. Post infusion angiography of the left ECA demonstrates normal antegrade flow.

Case 2

Medical History and Postinterventional Follow-up

This 32 year-old male patient with a history of multiple cranial and spinal tumors associated with neurofibromatosis type 2 presented with progressive bilateral hearing loss (left > right) and tinnitus for 1 year. MRI revealed bilateral T1 hypointense and T2 hypointense enhancing masses in the cerebellopontine angles with extension into the internal auditory canals. The masses measured 2.4 x 2.1 x 2.2 cm on the right and 2.8 x 3.1 x 3.1 cm on the left side (Figure 2A). Indication for IA BV treatment of the left sided lesion was made and the patient received 15mg/kg BV through the supplying tumor vessels. The postinterventional course was uneventful and the left sided hearing loss improved within a month. No adverse effects with regard to the IA BV administration were present in this patient. Follow-up MRI did not show any increase or decrease in the contrast-enhanced tumor size after 1 month and was therefore stable compared to the pre-

interventional measurements.

Supersensitive Intra-arterial Cerebral Infusion Treatment

As described in Case 1 endovascular technique was performed to explore the tumor supplying vessels. First the left MMA was displayed and PA and lateral projections demonstrated normal antegrade flow with some tumor blush arising from the left MMA. 10 cc of 25% mannitol was infused through the microcatheter over a period of 2 minutes. Then, 30 cc of 45cc BV (15 mg/kg) was infused through the microcatheter over 30 minutes. Post infusion angiography of the left ECA after mannitol and BV infusion demonstrated normal antegrade (Figure 2B).

In a second step, 10 cc of 25% mannitol was infused into the left AICA through an Excelsior SL 10 microcatheter over a period of 2 minutes. Post mannitol infusion, PA and lateral projections of the left AICA demonstrated normal antegrade flow with no evidence of vascular injury. Then, 15 cc of 45 cc BV (15 mg/kg) was infused through the microcatheter over 20 minutes (Figure 2C). Approximately two-thirds of BV concentration was administered into the left MMA and one-third into the left AICA.

Case 3

Medical History and Postinterventional Follow-up

A 31 year-old female presented with a long history of NF 2 and bilateral VS including complete left hearing loss and left facial nerve palsy since surgical tumor removal 3 years ago in a different hospital. Hearing on the right side was stable at the time of clinical presentation and IV BV treatment was started 2 months ago. An MRI revealed multiple small enhancing masses involving the skull base foramina and a large

heterogeneously enhancing extra-axial mass (4.2 x 2.5 x 2.9 cm) located in the right cerebellopontine angle extending into the internal auditory canal. The mass led to an enlargement of the porous acoustic and the adjacent right cerebellar hemisphere, brainstem and cerebellopontine angle was compressed (Figure 3A). Surgical removal of the right VS lesion was declined by the patient and indication for IA BV was made to ensure the right hearing capacity. Follow-up MRI 1 month after treatment showed a stable tumor size of 4.2 x 2.5 x 2.9 cm without any progression. No adverse effects with regard to the IA BV administration were present.

Superselective Intra-arterial Cerebral Infusion Treatment

With selective endovascular technique via the basilar artery the right AICA was explored and selective angiogram showed a moderate degree of tumor opacification. 10cc of 25% mannitol was infused through the microcatheter over a period of 2 minutes and post infusion angiography demonstrated anterograde flow into the right AICA and its branches. The tumor opacification was increased after mannitol infusion (Figure 3B). Next, 20 cc of Bevacizumab (15mg/kg) was infused through the microcatheter over 20 minutes. Using the same technique, an Excelsior SL 10 microcatheter with a 45 degree angle was advanced over a Synchro 2 soft microwire through the guide catheter into the right ECA and into the right MMA. A minimal degree of tumor opacification was visualized via petrosal branches arising from the right MMA (Figure 3C). Then, 10cc of 25% mannitol was infused through the microcatheter over a period of 2 minutes. Post infusion angiography demonstrated anterograde flow into the right MMA and its branches. Then, 14 cc of Bevacizumab (15mg/kg) was infused through the microcatheter

over 14 minutes for a total infusion time of 34 minutes. Approximately 60% of the Bevacizumab dose was infused into the right AICA and 40% of the dose into the right MMA.

Discussion

BV is a monoclonal antibody that binds to vascular endothelial growth factor (VEGF) and blocks the formation of new blood vessels, but also affects existing vasculature.[9] Anti-angiogenic therapy may normalize the structure and function of blood vessels and decrease tumor-related edema. Recent studies demonstrating the effectiveness of BV has established it as a possible treatment of VS.[6-8] Systemic toxicity has been noted with its use, including infections, venous thromboembolic events, and wound-healing complications. Our group hypothesized that intra-arterial BV would increase concentrations of the drug via local delivery of the anti-VEGF compound into the VS, thus leading to further reduction in tumor size and improvement in overall hearing, specifically word discrimination, in patients with NF 2. Especially, in hypervascular VS, as shown in case 3, endovascular SIACI of BV seems to be a promising approach to locally increase BV concentration.[15] In our study, we found a decreased tumor volume after 1 month in one patient and a stable tumor volume in the other two patients. Mautner et al. argued that radiographic regression is dependent on sustained administration of IV Avastin over time.[7] Therefore, follow-up studies are needed to assess the effect of more than one IA administrations over time. However in this study, we show for the first time that IA BV treatment was safe for all patients without any procedure related side-effects. We had no thromboembolic events, hemorrhage, congestive heart failure, gastrointestinal perforation, or delayed wound healing after IA BV treatment. The use of intra-arterial

delivery of chemotherapy has been shown to be advantageous to IV dosing in cerebral disease in both animal models of glioma and human studies.[16] In addition, techniques for BTB disruption with osmotic agents have been developed and safely utilized with chemotherapy infusion for over 20 years.

This case describes the first report of SIACI of an osmotic agent and BV for VS. The efficacy of BTB disruption is demonstrated by increased vascular hyperemia in the tumor after mannitol injection. This brief hyperemia allows for increased exposure of the monoclonal antibody BV to tumor vascular endothelial growth factor targets.

Conclusion

Recent studies suggest the efficacy profile of IV BV on VS in patients with NF 2. We have combined this treatment protocol with endovascular techniques to accurately and selectively disrupt the BTB before chemotherapy infusion. This technical report describes the method of SIACI of BV after BTB disruption for VS in patients with neurofibromatosis type 2. If proven safe and effective in a larger cohort of patients, this paradigm may significantly alter the way chemotherapies are delivered to patients with NF 2 and VS.

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Figure Legend

Figure 1: MRI (A) and digital subtraction angiogram (B) of a 56 year old man with bilateral VS. (A) The VS measure 1.3 x 1.9 x 1.2 cm on the right and 1.4 x 2.0 x 1.1 cm on the left side on T1 post-contrast MRI. (B) Lateral projections of the left AICA demonstrated normal antegrade flow after blood tumor barrier disruption with mannitol and BV infusion.

Figure 2: MRI (A) and digital subtraction angiogram (B, C) of a 32 year old man with bilateral VS. (A) The VS measure 2.4 x 2.1 x 2.2 cm on the right and 2.8 x 3.1 x 3.1 cm on the left side on T1 post-contrast MRI. Lateral projections of the left ECA (B) and left AICA (C) demonstrated normal antegrade flow after blood tumor barrier disruption with mannitol and BV infusion.

Figure 3: MRI (A) and digital subtraction angiogram (B, C) of a 31 year old female with NF 2. (A) T1 post-contrast MRI demonstrate a large right-sided VS measuring 4.2 x 2.5 x 2.9 cm. Lateral projections of the right AICA (B) and right MMA (C) demonstrated normal antegrade flow after blood tumor barrier disruption with mannitol and BV infusion.

Figure 1

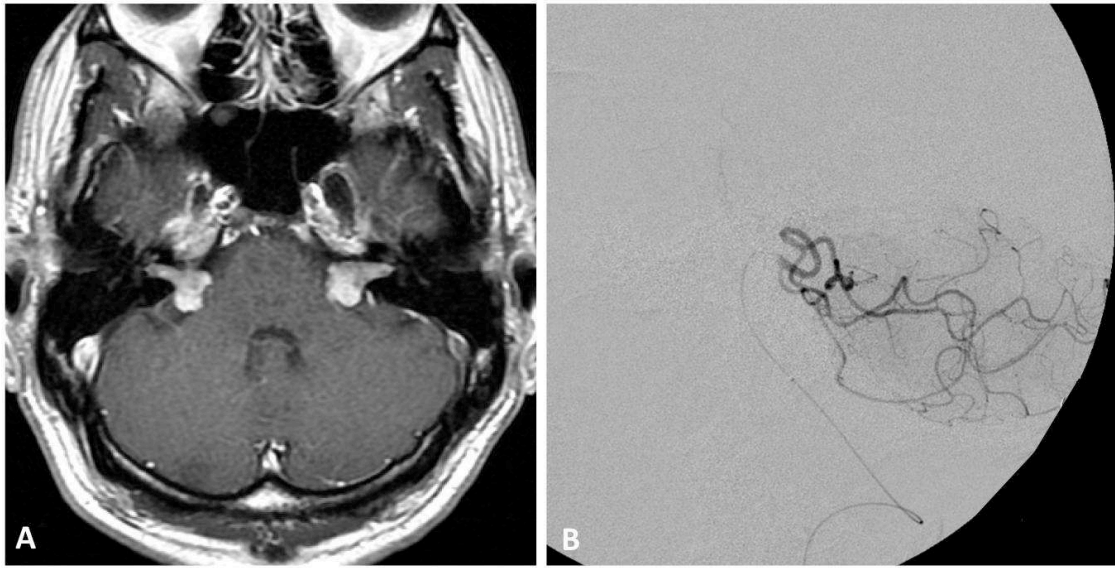


Figure 2

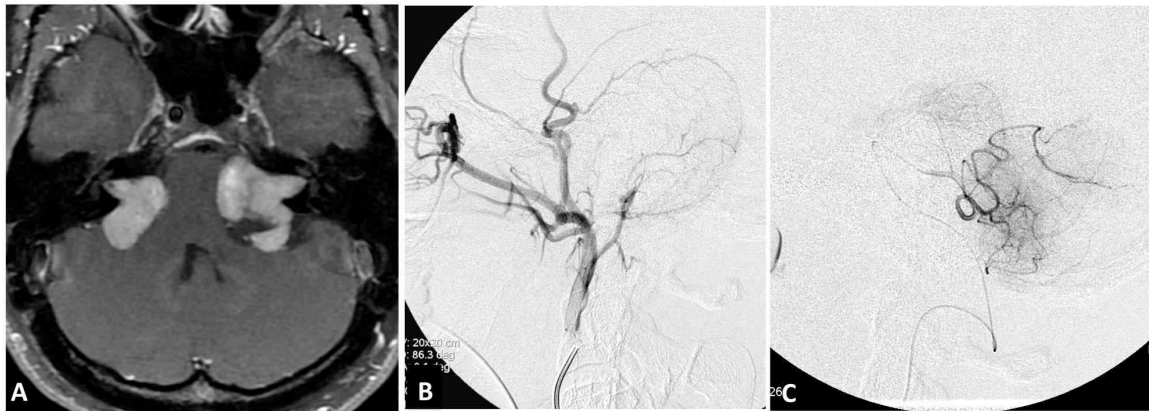


Figure 3

